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EAACI GUIDELINES ON ALLERGEN IMMUNOTHERAPY IgE-MEDIATED FOOD ALLERGY

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Food allergy can result in considerable morbidity, impairment of quality of life and healthcare expenditure. There is therefore interest in novel strategies for its treatment, particularly food allergy allergen immunotherapy (FA-AIT) through the oral (OIT), sublingual (SLIT) or epicutaneous (EPIT) routes. This Guideline, prepared by the European Academy of Allergy and Clinical Immunology (EAACI) Task Force on Allergen Immunotherapy for IgE-mediated Food Allergy, aims to provide evidence-based recommendations for active treatment of IgE-mediated food allergy with FA-AIT. Immunotherapy relies on the delivery of gradually increasing doses of specific allergen to increase the threshold of reaction while on therapy (also known as desensitization) and ultimately to achieve post-discontinuation effectiveness (also known as tolerance or sustained unresponsiveness). Oral AIT has most frequently been assessed: here the allergen is either immediately swallowed (OIT) or held under the tongue for a period of time (SLIT). Overall, trials have found substantial benefit for patients undergoing either OIT or SLIT with respect to efficacy during treatment, particularly for cow's milk, hen's egg and peanut allergies. A benefit post-discontinuation is also suggested, but not confirmed. Adverse events during AIT have been frequently reported, but few subjects discontinue FA-AIT as a result of these. Taking into account the current evidence, AIT should only be performed in research centers or in clinical centers with an extensive experience in food allergy AIT. Patients and their families should be provided with information about the use of AIT for IgE-mediated food allergy to allow them to make an informed decision about the therapy.

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INTRODUCTION

Food allergy (FA) has emerged as a significant medical problem in recent decades. With FA now affecting up to 8% of children and 5% of adults in westernised countries, development of therapies for this potentially life-threatening condition has become a public health priority (1-3). The key terms and clinical presentation of FA are summarised in Boxes 1 and 2. The current approach in managing FA focuses on avoidance of trigger foods and the availability of and training in the use of rescue medication in the event of an allergic reaction. Allergen immunotherapy (AIT) is potentially a curative therapy. AIT may increase the amount of food that the patient can tolerate, preventing allergic symptoms and reducing the risk of potentially life-threatening allergic reactions. The first case of immunotherapy for food allergy (FA-AIT) was described in 1908 to hen's egg (HE) (4); the principles underlying the therapy have remained the same, i.e. therapy consists of the administration of gradually increasing doses of food allergens via the oral, sublingual or subcutaneous routes (2). A fixed

dose of allergen can be administered through the epicutaneous route (2).

The ultimate goal of FA-AIT is to achieve post-discontinuation effectiveness so that a patient can eat a normal serving of the trigger food without symptoms. This is also known as “tolerance” or “sustained unresponsiveness”. These terms all imply that the food allergen can be ingested without the appearance of allergic symptoms despite a period of absence of exposure. The time period required to establish true post-discontinuation effectiveness is not yet defined. Based on current evidence, a more attainable target is effectiveness during treatment (typically referred to as “desensitisation”) which refers to a reversible or partially reversible clinical response that is dependent on ongoing allergen exposure. If the administration of the allergen is discontinued, the previous level of clinical reactivity may return (5).

The primary outcome of FA-AIT is a change in the threshold of allergen required to trigger an allergic reaction determined by an oral food challenge (OFC) - where possible, this is preferably a double-blind,

Box 1 Key terms

Allergen immunotherapy	Repeated allergen exposure at regular intervals to modulate immune response to reduce symptoms and the need for medication for clinical allergies and to prevent the development of new allergies. This is also known as allergen specific immunotherapy.
Effectiveness during treatment	The ability to safely consume foods containing the culprit allergen while on allergen immunotherapy. This clinical response is dependent on ongoing allergen exposure. If the administration of the allergen is discontinued, the previous level of clinical reactivity may return. This is also referred to as “desensitization”.
Food	Any substance, whether processed, semi-processed, or raw, which is intended for human consumption, and includes drink, chewing gum, and any substance which has been used in the manufacture, preparation, or treatment of ‘food’ but does not include cosmetics or tobacco or substances used only as drugs [<i>Codex Alimentarius</i>]. Food is eaten, drunk or otherwise taken to the body to provide energy and nutritional support, maintain life, or stimulate growth.
Food allergy	An adverse reaction to food mediated by an immunologic mechanism, involving specific-IgE (IgE-mediated), cell-mediated mechanisms (non-IgE-mediated) or both IgE- and cell-mediated mechanisms (mixed IgE- and non-IgE-mediated) [from EAACI Food Allergy and Anaphylaxis Guidelines (3)].
Post-discontinuation effectiveness	The ability to safely consume a normal serving of food containing the trigger allergen despite a period of absence of exposure. This is also known as “tolerance” or “sustained unresponsiveness”.
Sensitization	Detectable IgE antibodies, either by means of skin prick test or determination of serum specific-IgE antibodies.

Box 2 Clinical presentations of IgE-mediated food allergy

Systems	Symptoms
Cutaneous	pruritus, erythema/flushing, urticaria, angioedema, contact urticaria
Ocular	itching, redness, tearing, periorbital edema
Oropharynx	itching, dryness/discomfort, swelling of the oral cavity, lips, tongue and/or pharynx
Respiratory tract	nasal congestion, nasal pruritus, rhinorrhea, sneezing hoarseness, laryngeal edema, dysphonia, shortness of breath, cough, wheezing, chest tightness/pain
Gastrointestinal	abdominal pain, nausea, emesis, diarrhea
Cardiovascular/Neurological	tachycardia, hypotension, dizziness, loss of consciousness/fainting, seizures, incontinence
Multi-organ	anaphylaxis
Miscellaneous	sense of impending doom, uterine cramping/contractions

placebo-controlled, food challenge (DBPCFC). There is great variability in the threshold of exposure between different studies and for different foods (6, 7). Additional parameters have been studied in the monitoring of FA-AIT, including: skin prick tests (SPT) (8), specific-IgE (sIgE), IgG and IgG4 levels in serum (9). Some studies have also looked at basophil activation tests (BAT) (10), cytokines (e.g. IL-10, IL-5 and IFN- γ) (11, 12), and regulatory T-cells (13).

The most frequent route of administration of FA-AIT is the oral route where the allergen is either immediately swallowed (oral immunotherapy, OIT) or held under the tongue for a period of time (sublingual immunotherapy, SLIT). There are currently ongoing studies using the subcutaneous route (subcutaneous immunotherapy, SCIT) for peanut and fish allergies (14–16). Epicutaneous immunotherapy (EPIT) is also under investigation for peanut and cow's milk (CM); it involves application of patches containing food allergen onto the skin (17). In general, there has been no consistent formulation of food in FA-AIT studies conducted to date (18). Dilutions of unprocessed products, crude extracts and flours have been used. Some studies have been carried out with powdered or lyophilized products. Only a few have used food extracts with a quantification of major allergens prepared by pharmaceutical companies or hospital pharmacies (11, 19).

This Guideline has been prepared by the European Academy of Allergy and Clinical Immunology (EAACI) Task Force on Allergen Immunotherapy for

IgE-mediated Food Allergy. It is part of the EAACI Guidelines on Allergen Immunotherapy. This Guideline aims to provide evidence-based recommendations for the use of AIT in patients with diagnosed IgE-mediated FA. The primary audience are clinical allergists. This Guideline is also likely to be of relevance to other healthcare professionals (e.g. other doctors, nurses, dieticians, psychologists and paramedics) who are involved in the management of patients with food allergy and their families in any setting.

The development of this Guideline has been informed by a formal systematic review (SR) and meta-analysis on FA-AIT that included 31 trials studying 1259 patients. There were 25 randomised clinical trials (RCT) and 6 non-randomised controlled clinical trials (CCT). OIT was covered by 25 studies, SLIT was used in 5, and EPIT in 1. The food allergies most frequently studied were CM (16 studies), HE (11 studies), and peanut (7 studies) (18).

METHODOLOGY

This Guideline was produced using the Appraisal of Guidelines for Research & Evaluation (AGREE II) framework (20, 21), which is a structured approach to guideline production. This is designed to ensure appropriate representation of the full range of stakeholders, a careful search for and critical appraisal of the relevant literature, a systematic approach to the formulation and presentation of recommendations, and steps to ensure that the risk of bias is minimised

Box 3 Summary of the aims and outcomes of the supporting systematic review (18)

Aim	To provide a systematic review of the evidence on the effectiveness, safety and cost-effectiveness of AIT for IgE-mediated food allergy.
Outcomes of the SR:	<p>Primary</p> <ul style="list-style-type: none">• Effectiveness during the treatment (i.e. the ability to safely consume foods containing the allergen in question while on AIT) or post-discontinuation effectiveness (the ability to consume foods containing the allergen in question after discontinuing AIT) at food challenge.• Assessment of changes in disease specific quality of life (QoL) using a validated instrument. <p>Secondary</p> <ul style="list-style-type: none">• Secondary outcome measures of interest were safety as assessed by local and systemic reactions in accordance with the WAO grading system of side-effects• Health economic analysis from the perspective of the health system/payer as reported in studies.

at each step of the process. The process started in April 2015 beginning with detailed face-to-face discussions agreeing on the process and the key clinical areas to address, followed by face-to-face meetings and web-conferences in which professional and lay representatives participated.

Clarifying the scope and purpose of the Guidelines

This Guideline aims to assist qualified clinicians in the optimal use of AIT in the management of patients with IgE-mediated FA, and highlight gaps for further research.

Ensuring appropriate stakeholder involvement

Participants in the EAACI Taskforce on FA-AIT represented a range of 16 countries, and different disciplinary and clinical backgrounds, including allergists, paediatricians, primary care physicians, immunologists and patient group representatives. Additionally, producers of AIT products were given the opportunity to review and comment on the draft Guideline.

Systematic review of the evidence

The initial full range of questions that were considered important were rationalized through several rounds of iteration to agree one key question: what is the effectiveness, changes in disease-specific quality of life (QoL), cost-effectiveness and safety of AIT in patients with IgE-mediated FA. This was then pursued

through a formal SR of the evidence by independent methodologists as previously published (18) (Box 3). We continued to track evidence published after our SR cut-off date of 31st March 2016 and, where relevant, recent studies were considered by the Taskforce’s joint Chairs. This most recent evidence will formally be considered in the SR update that will precede the update of this Guideline.

Formulating recommendations

We assessed the strength, consistency and quality of evidence in relation to key findings from the SR and meta-analyses (18) (which were undertaken using random-effects models to take into account the heterogeneity of findings) to formulate evidence-based recommendations for clinical care (Box 4) (22). This involved formulating clear recommendations with the strength of evidence underpinning each recommendation. Where the SR did not cover the clinical area, we took a hierarchical approach reviewing other evidence until we could formulate a recommendation, i.e. (i) other SRs on the subject to see if these provided any clarity on the topic; (ii) RCTs within these systematic reviews; (iii) other RCTs known to Taskforce members; and (iv) an expert consensus-based approach. This evidence was also assessed, as described above. Experts identified the resource implications of implementing the recommendations, barriers, and facilitators to the implementation of each recommendation, advice on approaches to implementing the recommendations and suggested audit criteria that can help with assessing organisational compliance with each recommendation.

Box 4 Assigning levels of evidence and recommendations

LEVEL OF EVIDENCE	
Level I	Systematic reviews, meta-analysis, randomized controlled trials
Level II	Two groups, non-randomized studies (e.g., cohort, case-control)
Level III	One group non-randomized (e.g., before and after, pre-test, and post-test)
Level IV	Descriptive studies that include analysis of outcomes (single-subject design, case series)
Level V	Case reports and expert opinion that include narrative literature, reviews, and consensus statements
GRADES OF RECOMMENDATION	
Grade A	Consistent level I studies
Grade B	Consistent level II or III studies or extrapolations from level I studies
Grade C	Level IV studies or extrapolations from level II or III studies
Grade D	Level V evidence or troublingly inconsistent or inconclusive studies at any level
STRENGTH OF RECOMMENDATIONS	
Strong	Evidence from studies at low risk of bias
Moderate	Evidence from studies at moderate risk of bias
Weak	Evidence from studies at high risk of bias

Recommendations are phrased according to the strength of recommendation: strong, “is recommended”; moderate, “can be recommended”; weak, “may be recommended in specific circumstances”; negative, “cannot be recommended”.

Approach adapted from Oxford Centre for Evidence-based Medicine - Levels of Evidence and Grades of Recommendations (22). The adaptation involved providing an assessment of the risk of bias, based on the Cochrane risk of bias tool, of the underpinning evidence and highlighting other potentially relevant contextual information.

Peer review and public comment

A draft of this Guideline was externally peer-reviewed by invited external experts from a range of organisations, countries, and professional backgrounds. Additionally, the draft Guideline was made available on the EAACI Website for a 3-week period in May 2017 to allow a broader array of stakeholders to comment. All feedback was considered by the Taskforce and, where appropriate, final revisions were made in light of the feedback received. We will be pleased to continue to receive feedback on this Guideline, which should be addressed to the corresponding author.

Identification of evidence gaps

The process of developing this Guideline has identified a number of evidence gaps which we have prioritised.

Editorial independence and managing conflict of interests

The production of this Guideline was funded and supported by EAACI. The funder did not have any influence on the guideline production process, on its contents, or on the decision to publish. Taskforce members' conflict of interests were taken into account by the Taskforce Chairs as recommendations were formulated. Final decisions about strength of evidence for recommendations were reviewed by methodologists who had no conflict of interests in this area.

Updating the guidelines

We plan to update this Guideline in 2021 unless there are important advances before then.

GENERAL CONSIDERATIONS BEFORE INITIATING AIT FOR IgE-MEDIATED FOOD ALLERGY

AIT is potentially indicated for patients with evidence of an IgE-mediated FA and in whom avoidance measures are ineffective, undesirable or cause severe limitations to a patient’s QoL. Prior to initiating AIT, confirming the diagnosis of IgE-mediated FA is mandatory. This requires a recent, clear clinical history of an acute reaction(s) after consumption of the triggering food. The presence of IgE to the triggering food should be established with SPT and/or sIgE. Where the diagnosis is unclear, an OFC is required. The baseline reaction threshold may be used to establish the efficacy of AIT in individual patients (Box 5).

Studies to date have enrolled patients with heterogeneous ages and clinical presentations (18). Studies have included infants and pre-school children who have tolerated FA-AIT safely (23, 24). However, the limited ability of young children to report early symptoms of allergic reactions should be considered. Furthermore, young children have a high likelihood of developing spontaneous tolerance, particularly to CM, HE, wheat and soy (25-31). Therefore, it might be more appropriate to wait for the natural acquisition of spontaneous tolerance before commencing AIT for these allergens (25-31). The right time to start may be around 4-5 years of age, but this should be decided on an individual basis.

FA-AIT is logistically demanding, time-consuming and most patients are affected by side effects. These are usually mild, but systemic reactions - including life-threatening anaphylaxis - may occur. AIT for FA should therefore only be undertaken in centres with professional training in FA care with the expertise, competencies and full resuscitation facilities to safely deliver this therapy and manage any complications, including anaphylaxis (Box 6). Only patients and families who understand the aim of the intervention and its risks, and are motivated and adherent should be considered for FA-AIT (Boxes S1 and S2 in the online). There are therefore many issues to be considered and discussed with the patient and family before commencing FA AIT (Box 7).

Box 5 Diagnosis of IgE-mediated food allergy before initiating FA-AIT

- Detailed medical history to establish current clinical reactivity to the food (recent reactions)
- Allergy testing (skin prick tests-SPTs, with food allergen extracts or fresh foods) and/or specific IgE (sIgE) to food allergen extract(s) or component(s) (component resolved diagnosis, CRD)
- Oral food challenge (OFC)

Box 6 Personnel and equipment required to perform FA-AIT

Personnel	Medical doctor and nurse trained and experienced in the diagnosis of food allergy including oral challenges, and trained and experienced in the recognition and treatment of allergic reactions including anaphylaxis. Personnel should be able to provide at least 12 hours of observation in case of adverse reactions related to AIT. #Anesthesiology team or intensive care or equivalent team particularly trained in resuscitation on call, at hand within 5 minutes.
Equipment	Stethoscope Sphygmomanometer Pulse oximeter Oxygen Spirometer, peak flow meter Laryngoscope(s), intubation tube(s), ventilation bag(s) Heart defibrillator (knowledge and experience how to use it) #Crash trolley
Medication	Adrenaline (epinephrine), antihistamine (oral and parenteral), inhaled beta2-agonist, corticosteroids (oral, parenteral). IV lines and IV fluids

According to the local facilities and organization of assistance to patients experiencing severe anaphylaxis.

Box 7 General considerations before initiating FA-AIT

Confirmed, persistent, systemic IgE-mediated FA.

Consider the likelihood of spontaneous resolution of the specific FA (e.g. CM and HE allergies)

Patients and their families should be motivated, adherent and capable of administering emergency treatment (including intramuscular adrenaline) in case of adverse effects

Clinical centres undertaking FA-AIT should have the expertise and facilities to safely deliver this therapy.

Box 8 General contraindications to FA-AIT

- Absolute**
- Poor adherence
 - Uncontrolled or severe asthma
 - Active malignant neoplasia(s)
 - Active systemic, autoimmune disorders
 - Active EoE or other gastrointestinal eosinophilic disorders
 - Initiation during pregnancy

- Relative** FA-AIT should only be used with caution in an individual patient when benefits outweigh potential risks
- Severe systemic illness or severe medical conditions such as cardiovascular diseases
 - Systemic autoimmune disorders in remission/organ specific (i.e. thyroiditis)
 - Uncontrolled active atopic dermatitis/eczema
 - Chronic urticaria
 - Beta-blockers
 - ACE inhibitors
 - Mastocytosis

GENERAL CONTRAINDICATIONS

Given the long-treatment duration and common adverse reactions, any medical or social condition that might prevent patients attending frequent clinical visits, being aware of side effects or adhering to treatment represents an absolute contraindication. Uncontrolled asthma is also an absolute contraindication as it is associated with an increased risk of life-threatening systemic reactions (32). Well-controlled asthma is however not a contraindication for FA-AIT. Although a history of moderate to severe anaphylaxis to a food may be associated with more side effects, it is not a contraindication; these patients require appropriate evaluation before starting FA-AIT and close supervision particularly during the build-up phase. Uncontrolled, severe atopic dermatitis/eczema and chronic urticaria are relative contraindications given the risk of acute exacerbation while on AIT and because they can confound safety assessment of AIT. Therefore, both disorders should be controlled before AIT is initiated. The presence of eosinophilic esophagitis (EoE) or any other eosinophilic gastrointestinal disease is a contraindication for FA-AIT because of the risk these worsen whilst on FA-AIT (33, 34).

There is a lack of available data on the risks associated with FA-AIT in autoimmune disorders, severe medical conditions such as cardiovascular diseases, mastocytosis, or with the concomitant use of medications such as beta-blockers or angiotensin-converting enzyme (ACE) inhibitors. However, the risk in other types of AIT has been assessed (35-

39); these conditions can be considered relative contraindications, and FA-AIT should only be used with caution when likely benefits outweigh risks (Box 8). The final decision about starting AIT should be established on an individual basis in discussion with the patient and/or family.

EFFECTIVENESS OF DIFFERENT APPROACHES TO AIT FOR IgE-MEDIATED FOOD ALLERGY

The effectiveness of FA-AIT has to be assessed in relation to the culprit food and route of administration.

Effectiveness of oral immunotherapy

A recently performed SR identified 23 trials: 18 RCTs and 5 CCTs (18). A meta-analysis of 22 of these trials involving 982 subjects revealed a substantial benefit for the patients (children and mixed population) undergoing OIT with CM, HE and peanut with respect to efficacy during treatment (RR 0.14, 95% CI 0.08, 0.24) (18).

There were 7 studies included in the SR (18) that assessed post-discontinuation effectiveness, but only 4 studies could be included in the meta-analysis (8, 40-42). This analysis suggested but did not confirm the longer-term benefits of OIT (RR 0.29, 95% CI 0.08, 1.13) (18). These 4 trials covered HE (8, 40-42) (169 subjects) and CM (40) (25 subjects), and assessed effectiveness by an oral challenge performed after 1 to 3 months of discontinuation of OIT. No subgroup analysis on the type of food or period of discontinuation could be performed. In an egg OIT trial, published after our SR (43), post-discontinuation effectiveness of egg OIT was enhanced with duration of OIT; however, there was no control group in the follow-up period to compare with natural resolution of the egg allergy. In this trial children were treated for up to 4 years, whereas those included in the meta-analysis were treated for a shorter period of time.

Regimens for OIT varied widely from rush protocols to slow up-dosing regimens with or without an initial dose escalation day (18). There was no apparent difference regarding effectiveness during treatment between CM, HE and peanut, and between the different protocols with all showing substantial effectiveness during treatment (18). The data published to date do not allow the ideal treatment regimen, including doses and intervals, to be determined. Additionally, the definition of effectiveness (i.e. increment of threshold) and its assessment varied among studies, and so the overall magnitude of the effect cannot be established. In conclusion, FA-OIT is recommended for persistent CM, HE or peanut allergy for children from around 4 to 5 years of age on the basis of its ability to increase the threshold for clinical reactions while on OIT (Grade A) (Table 1-3). At present, there are insufficient data to be able to recommend AIT for other foods (Table 4) and for adults outside clinical trials (Table 5).

Effectiveness of sublingual immunotherapy

There are few published studies which have assessed the effectiveness of SLIT. A recent meta-analysis identified four placebo-controlled RCTs and one CCT for the assessment of efficacy of SLIT while on therapy (18). The total number of patients treated was limited (n=189), and the food allergies covered included peanut (12, 52), hazelnut (11), and peach (53) in RCTs, and different foods in a CCT (50) (RR=0.26, 95% CI 0.10, 0.64). Overall, SLIT revealed substantial benefits for the patients in regard to desensitization (18),

Table 1 Recommendations on efficacy of OIT in children with persistent cow’s milk allergy

Recommendations*	Evidence level	Grade of recommendation	Strength of recommendation	Other considerations	Key references
OIT is recommended as a treatment option to increase threshold of reaction while on treatment in children with persistent cow’s milk allergy, from around 4 - 5 years of age.	I	A	Strong recommendation based on convincing evidence from SR and meta-analysis (18) including RCTs at low (7, 9) or unclear risk of bias (44)	Risk of adverse reactions needs to be considered. Age recommendation is based on expert opinion.	Nurmatov 2017 (18); Longo 2008 (7); Pajno 2010 (9); Skripak 2008 (44)
A recommendation cannot currently be made for OIT as a treatment option in children with persistent cow’s milk allergy with the goal of post discontinuation effectiveness.	I	B	Weak as only one small RCT at high risk of bias (40)	Further studies needed	Staden 2007 (40)

* OIT for food allergy should only be undertaken in highly specialised clinical centres with expertise and facilities to safely deliver this therapy.

Table 2 Recommendations on efficacy of OIT in children with hen's egg allergy

Recommendations*	Evidence level	Grade of recommendation	Strength of recommendation	Other considerations	Key references
OIT can be recommended as a treatment option to increase the threshold of reaction while on OIT in children with persistent hen's egg allergy, from around 4 - 5 years of age.	I	B	Moderate recommendation based on evidence for effect from SR and meta-analysis (18) including low risk of bias RCTs (8, 42). Studies are all small with some heterogeneity in results.	Risk of adverse reactions needs to be considered. Age recommendation is based on expert opinion. Additional large studies required.	Nurmatov, 2017 (18); Burks, 2012 (8); Caminiti 2015 (42)
A recommendation cannot currently be made for OIT as a treatment option to achieve post-discontinuation effectiveness in children with persistent hen's egg allergy	I	B	Strong recommendation based on only one RCT with low risk of bias (43)	After 4 years of OIT 50% of subjects achieved sustained unresponsiveness 4-6 weeks after stopping OIT (43). Further studies needed.	Jones 2016 (43)

* OIT for food allergy should only be undertaken in highly specialised clinical centres with expertise and facilities to safely deliver this therapy.

Table 3 Recommendations on efficacy of OIT in children with persistent peanut allergy

Recommendations*	Evidence level	Grade of recommendation	Strength of recommendation	Other considerations	Key references
OIT is recommended as a treatment option to increase the threshold of reaction while on treatment in children with peanut allergy from around 4-5 years of age	I	A	Strong recommendation based on consistent evidence from SR and meta-analysis (18) with low risk of bias RCTs (45-47)	Risk of adverse reactions to be considered. Age recommendation is based on expert opinion.	Nurmatov 2017 (18); Narisety 2015 (45); Tang, 2015 (46); Varshney 2011 (47)
A recommendation cannot currently be made for OIT as a treatment option to achieve post discontinuation effectiveness in children with peanut allergy	I	B	Strong recommendation based on two RCTs at low risk of bias (23, 45)	Inconsistent study results. Further studies needed.	Vickery 2017 (23), Narisety 2014 (45)

* OIT for food allergy should only be undertaken in highly specialised clinical centres with expertise and facilities to safely deliver this therapy.

Table 4 Recommendations on efficacy of OIT in children with persistent allergies to other foods

Recommendations*	Evidence level	Grade of recommendation	Strength of recommendation	Other considerations	Key references
A recommendation cannot currently be made for OIT as a treatment option to increase the threshold of reaction while on treatment in children allergic to other foods (e.g. fish, wheat, peach)	II	B	Weak recommendation based on a few cases reported in one RCT at high risk of bias (48) and two CCTs at moderate risk of bias (49, 50)	Risk of adverse reactions to be considered	Patriarca, 1998 (48), Patriarca, 2003 (49); Patriarca, 2007 (50)

* OIT for food allergy should only be undertaken in highly specialised clinical centres with expertise and facilities to safely deliver this therapy.

Table 5 Recommendation on efficacy of OIT in adults with persistent food allergy

Food	Recommendations	Evidence level	Grade of recommendation	Strength of recommendation	Other considerations	Key references
Cow's milk	No recommendation can be made about OIT as a treatment option in adults with persistent cow's milk allergy	V	D	No recommendation due to lack of evidence		
Hen's egg	No recommendation can be made about OIT as a treatment option in adults with persistent hen's egg allergy	V	D	No recommendation due to lack of evidence		
Peanut	No recommendation can be made about OIT as a treatment option in adults with peanut allergy	II	B	Weak as only one CCT including mixed populations (51). No recommendation due to lack of evidence.		Syed 2014 (51)
Others	No recommendation can be made about OIT as a treatment option in adults allergic to other foods (e.g. fish, wheat, peach)	V	D	No recommendation due to lack of evidence.		

but none of the studies included in the SR assessed post-discontinuation effectiveness. However, an open follow-up of a peanut SLIT trial in children and adults found only 11% of patients achieving tolerance after three years on SLIT and post-discontinuation of the AIT for 4-6 weeks (54).

Head-to-head trials of OIT versus SLIT

Two trials directly compared the efficacy of OIT and SLIT: the first focused on CM (55) and the second on peanut allergy (45). The first trial randomized 30 children with CM allergy to SLIT alone or SLIT followed by OIT. This trial clearly showed that OIT after SLIT was more efficacious for desensitization and sustained unresponsiveness after six weeks off therapy to CM than SLIT alone (55). The second trial was a double-blind study involving 21 children with peanut allergy who were randomized to receive either active SLIT/placebo OIT or active OIT/placebo SLIT. As in the CM trial, OIT was far more effective than SLIT for the treatment of peanut allergy as the increased threshold was significantly greater in the active OIT group while on therapy (45). OIT would seem to be a better therapeutic option than SLIT, but it is associated with significantly more adverse reactions. Currently, we cannot recommend SLIT for FA due to the limited effectiveness.

Other routes of AIT under investigation

EPIT with unmodified allergens is currently under investigation for peanut and CM. Efficacy results of one placebo controlled RCT with peanut EPIT in 74 subjects aged 4-25 years have shown an increase in the threshold of reaction while on therapy. This effect was higher in patients younger than 11 years of age (17). Moreover, SCIT with modified allergens is also under development (14-16). Two SCIT trials are currently ongoing: one using a chemically modified peanut extract (14) and another one using hypoallergenic recombinant parvalbumin for fish allergy (16). And finally, a phase 1 trial with modified peanut allergens administered by the rectal route has been conducted, but showed significant side effects, which led to early termination of the trial (56). At present, we cannot recommend EPIT or SCIT for FA-AIT.

SAFETY OF AIT

Alongside efficacy, safety is pivotal to any treatment. In AIT, safety is particularly important, as potential adverse events are mostly immediate onset, food-induced IgE-mediated reactions, which can lead to anaphylaxis. Events related to safety have been highlighted in the studies addressed by the SR (18). The heterogeneity in the reporting formats reduced the number of studies that could be pooled in the meta-analysis. Despite this, it was shown that patients receiving the active preparation experienced significantly more reactions, both systemic and local, than those who received placebo (18). Recommendations on safety of AIT are shown in Table 6.

Oral immunotherapy

OIT to foods is associated with a large number of local reactions. These are mainly itching of the oropharynx, perioral rash, and mild abdominal pain and can be bothersome when they occur repeatedly. Local reactions may evolve into more severe systemic reactions, but only a minority of patients experiences these. Results for systemic reactions from five OIT studies and for local reactions from 7 studies were pooled in the meta-analysis. Patients receiving active treatment had a higher risk of systemic reactions than those in the placebo group (RR of not experiencing a systemic reaction in controls: 1.16, 95% CI 1.03, 1.30) (18). OIT was also associated with a higher risk of local reactions (RR of not experiencing a local reaction in controls: 2.14, 95% CI 1.47, 3.12) (18). No deaths have been reported in the meta-analysis (18). It is therefore recommended that patients are carefully monitored for local and systemic allergic reactions in FA-AIT, particularly during the up-dosing phase of FA-OIT (Grade A).

Dosing with an empty stomach, irregular intake, exercise, infection, medication use, menses, and suboptimal control of asthma or of allergic rhinitis may increase the risk of reactions (59-63) especially during the maintenance phase(s) of OIT, when patients continue treatment at home. Although adverse reactions have been reported in the absence of these co-factors, patients should be informed and instructed on how to manage AIT in these situations (Boxes 9 and 10). It is recommended that a careful evaluation and explanation to the patient and his/her caregiver(s) of the risk of reactions during FA-AIT is undertaken before starting AIT (Grade C) (Table 6).

Table 6 Recommendations on safety of FA-AIT

Recommendations	Evidence level	Grade of recommendation	Strength of recommendation	Other considerations	Key references
It is recommended to carefully monitor patients for local and systemic allergic reactions in FA-AIT particularly during the up-dosing phase of FA-OIT	I	A	Strong recommendation based on SR and meta-analysis (18) including RCTs at low risk of bias (9, 42)		Nurmatov, 2017 (18); Pajno 2010 (9); Caminiti 2015 (42)
It is recommended to monitor patients for symptoms of new onset eosinophilic esophagitis which may appear in the course of FA-OIT	I	B	Moderate recommendation based on SR (33) including one RCT and case reports.		Lucendo 2014 (33)
A careful evaluation and explanation to the patient and his/her caregiver(s) of the risk of reactions during FA-AIT is recommended before starting AIT	V	D	Moderate recommendation based on the risks identified by experts in RCTs at low (7) and unclear risk of bias (40)		Longo 2008 (7); Skripak 2008 (44)
A careful evaluation of levels of sIgE, SPT and concomitant asthma control is recommended before starting FA-AIT as high levels of sIgE and skin reactivity, and asthma have been found as risk factors for adverse events.	IV	C	Weak as based on expert review of consistent observational data (57-61)	Individual predictors of severe reactions still need to be identified	Vazquez-Ortiz, 2013 (57); Vazquez-Ortiz, 2014 (58); Martínez-Botas (59); Varshney 2009 (60); Narisety 2009 (61)

Box 9 Summary of the management

- Provision of individualized schedule, clearly written in simple non-medical language. It should include personal identification data (name, address, contact details of the parents, guardian, a next of kin, and family doctor).
- Copy of schedule should be kept by the patients or his/her caregiver(s), and their family doctor.
- Clear identification of food allergen to be administered during FA-AIT.
- Clear explanation that FA-AIT escalation dose(s) has to be administered in clinical specialized setting under strict medical supervision properly equipped for treatment of potentially severe allergic reactions.
- The risk of reaction caused by FA-AIT should be explained to the patient and his/her caregiver before starting FA-AIT.
- Provision of emergency kit with copy of emergency action plan and adrenaline auto-injector for treatment of anaphylaxis.

Box 10 Practical recommendations for patients

- Take dose daily
- Do not take dose on an empty stomach
- Do not go to the bed in the hour following a dose
- Do not do exercise in the 2-3 hours following a dose
- Reduce or withhold the dose during infections, asthma exacerbations, gastrointestinal diseases or menses.

Additionally, a careful evaluation of levels of sIgE, SPT and concomitant asthma control is recommended before starting FA-AIT as high levels of sIgE and skin reactivity, and asthma have been found as risk factors for adverse events (Grade B) (Table 6).

Dose adaptations are made according to the severity of allergic reactions. In mild reactions, doses can remain the same according to the protocol. With repeated mild reactions, particularly when bothersome to the

patient, dose increments may be stopped, or doses may even be reduced. With systemic reactions, doses are usually reduced, although it is not established if a reduction is necessary in all patients, particularly when reactions only develop in the presence of co-factors. In patients with systemic reactions, individualized schedules with a longer and slower up-dosing phase, and premedication (antihistamines, or omalizumab) may be considered (58). We suggest a case-by-case evaluation of dose adaptation, and a thorough review of any underlying condition. The control of any concomitant allergic disease, and especially asthma, has to be optimal. Safety should remain the priority.

Sublingual immunotherapy

SLIT is associated with a lower risk of significant adverse events than OIT. In RCTs of SLIT (11, 12, 52-54), systemic reactions have been uncommon (<0.5-2.3% of doses) and generally mild, and appeared not to differ from those observed in the placebo treated patients. Meta-analysis of 2 SLIT studies (11, 53) did not show a significantly higher risk of systemic reactions in the active group (RR of not experiencing a systemic reaction in controls: 0.98, 95% CI 0.85, 1.14) (18). The most common adverse events in SLIT trials were mild local reactions in the oropharynx (7-40% of patients), which can be observed during both the up-dosing and maintenance phases. A meta-analysis of local reactions with SLIT could not be undertaken due to different formats in reporting reactions between trials.

SCIT and EPIT

The experience with SCIT using whole peanut aqueous allergen extracts is limited, mostly due to the high number of severe adverse events (including severe anaphylaxis) (64, 65). SCIT studies are currently underway with hypoallergenic recombinant parvalbumin and chemically modified peanut extract. These modified allergens have reduced allergenicity, but their safety profiles have not been yet reported (14-16).

One phase II RCT of EPIT with peanut suggests a favorable safety profile (17). Although patch-site reactions were observed in more than 90% of active treated patients, most were mild. Non-patch-site reactions were observed in less than 20% of patients, were also mild and responded to oral antihistamines or topical corticosteroids. No reactions required adrenaline.

The clinical setting for food allergy AIT

FA-AIT should only be undertaken in a setting where the full spectrum of food allergy reactions - including life-threatening anaphylaxis - can be managed (Boxes 6 and table 6). In particular, administration of initial doses and regular increments requires the presence of staff trained to manage anaphylaxis. Doses tolerated in the clinical setting are subsequently taken at home. Patients need clear instructions on how to detect an allergic reaction and its appropriate self-management. They also need to have on-hand appropriate medications including adrenaline auto-injectors. All dose increments have to be performed in a clinically specialized setting, and if no reactions are observed the same dose can be subsequently taken at home.

When to stop AIT after adverse reactions?

With repeated local adverse reactions and/or systemic adverse events, discontinuation of AIT should be discussed with the patient and/or family.

Long-term safety

Long-term safety is not addressed in trials; these predominantly focus on efficacy and short term safety. The development of EoE after OIT has been reported (33, 34, 62, 66). In a SR, new onset EoE was found in 2.7% (95% CI 1.7, 4.0). All the studies analyzed were retrospective with significant publication bias suggested by funnel plot analysis (33). It is therefore recommended to monitor patients for symptoms of new onset EoE which may appear in the course of FA-OIT (Grade A).

ALLERGEN FACTORS THAT AFFECT THE EFFECTIVENESS AND SAFETY OF AIT

In the SR on FA-AIT, the majority of trials were on CM (n=16), HE (n=11) and peanut (n=7), with only 1-3 studies for each of the other foods (18). AIT for CM, HE and peanut had similar efficacies in terms of desensitization with RR of 0.12 (95% CI 0.06, 0.25), 0.22 (0.11, 0.45) and 0.11 (0.04, 0.31), respectively. Of note, in these pooled analyses, the majority of studies were OIT with just a few SLIT ones and the products differed (e.g. peanut flour for OIT versus a peanut extract for SLIT).

Seven trials on different foods (3 CM, 1 HE, 1 peanut, 1 peach and 1 hazelnut; the latter two dealing with SLIT, and the remaining 5 with OIT) could be pooled for analysis regarding occurrence of systemic reactions. An increased risk of systemic reactions was observed with OIT, but a comparative subgroup analysis on the type of allergen could not be undertaken (18). For local reactions, milk seems more prone to cause side effects than egg although no statistically significant differences were found between them (milk 2.70, 1.33, 5.47; egg 1.55, 1.09, 2.22) (18). In conclusion, there is no evidence that the efficacy and safety are affected by the type and nature of the food allergen used in AIT.

PATIENT FACTORS THAT AFFECT THE EFFICACY AND SAFETY OF AIT

Different patient factors have been suspected to affect the outcomes of FA-AIT, both in terms of efficacy and safety. Concerning patient age, the SR and meta-analysis found that FA-AIT is effective in reducing FA in children and a population of mixed ages with IgE-mediated FA to a range of foods. It is still unclear if AIT is effective for adults. There are no studies of OIT performed exclusively in adults and in those performed with mixed (i.e. children and adult) populations, efficacy could not be analyzed separately according to age (18). The only studies focused on adults used SLIT with hazelnut and peach, and showed an increase in threshold of reaction while on therapy (11, 53).

In the SR and meta-analysis on FA-AIT, there were insufficient data to analyze the role of other patient factors such as the number of culprit foods of clinical relevance, co-existence of asthma or other severe allergic disorders, on FA-AIT outcomes (18). Some studies have shown that patients with greater IgE-sensitisation, lower threshold/higher severity and associated asthma are those with a higher frequency of adverse events (57, 58, 62). In a similar vein, some studies found that smaller SPT wheal size and lower sIgE levels have been associated with an increased likelihood of achieving desensitization and tolerance (67, 68). However, other studies did not find a significant correlation between pre-FA-AIT SPT/ sIgE

results and treatment success (45, 52), and some FA-AIT studies have included children with severe FAs or anaphylaxis with elevated sIgE who were successfully treated with FA-AIT (7, 9). Two studies performed in children allergic to CM have shown that IgE recognition of peptides of CM proteins are biomarkers that predict safety and efficacy of CM-AIT (54, 61).

ADHERENCE TO AIT

Adherence to treatment is a crucial consideration both to ensure efficacy and safety of FA-AIT. Given that FA-AIT is time-consuming and burdened by potential side effects, patients and their families must be extremely adherent, reliable and committed to a treatment regimen that may cover a long period of time. Given these premises, poor adherence to the treatment is an absolute contraindication (Box 8). A clear and detailed explanation about the FA-AIT procedure (i.e. up-dosing schedules, setting), the related outcomes and risk of side effects, together with getting information on patients' and/or families' opinions and expectations are pre-requisites to the inclusion in the treatment protocol. Patients and their families need to be supported during the entire treatment. Informed consent should be signed by patients (where appropriate) and their parents.

SUMMARY, GAPS IN THE EVIDENCE AND FUTURE PERSPECTIVES

FA-AIT represents the active treatment of IgE-mediated FA instead of avoidance and rescue drug management. The usual management of FA demands changes in eating habits with serious repercussions on QoL, potential risk of nutritional deficiencies, especially in young children, and severe adverse reaction in case of accidental exposure to the culprit food.

The recent SR and meta-analysis on FA-AIT (18) clearly demonstrated that FA-AIT is effective in reducing the likelihood of reacting to foods while receiving the therapy. In pediatric patients with FA to CM and peanut, data suggest that OIT is more effective than SLIT (45, 55). There is an increased risk of local (the most frequent) reactions with both OIT and SLIT but only OIT showed a significantly higher risk of systemic

reactions. Due to the length of the protocol and safety issues, patients and their families must be extremely adherent, reliable and committed to the treatment. FA-AIT may improve QoL scores, particularly with regard to social limitations, accidental exposure and anxiety, although further studies are needed (5).

Many children with CM allergy or HE allergy develop tolerance spontaneously. For this reason, for many patients and families, allergen avoidance whilst awaiting spontaneous resolution may represent a better option than FA-AIT. Therefore, FA-AIT cannot be recommended as routine practice, but must be limited only to carefully selected patients managed in specialized clinical settings, by trained personnel (Boxes 9 & 10).

There are still many gaps that need to be addressed (Table 7). The duration of FA-AIT may be burdensome for patients and their families. After completion of therapy, patients frequently need to continue to consume the allergen to maintain tolerance. It may be easier to achieve post-discontinuation effectiveness (e.g. tolerance or sustained unresponsiveness) for allergens that are typically outgrown in childhood (e.g. CM and HE) compared to other allergens (such as peanut), where probably lifelong ingestion may be required after therapy. In addition, efficacy during the treatment with CM can be maintained with a twice-weekly regimen. We await maintenance follow-up studies to assess whether more flexible regimens are possible with other foods (69).

The quality of allergen preparations is critical for both diagnosis and treatment. Standardized allergen preparations of known potency and shelf-life should be used. Currently, the allergens containing food protein and those prepared by pharmaceutical companies or hospital pharmacies are not available as standardized products. The allergens in such products should be well characterized as it is known that different formulations of a product may have significant variations in allergen load. Both the bacteriological load and biological activity of these products are still undetermined. Therefore, the use of fresh material or native foods for FA-AIT is advisable to achieve the goal of desensitization. Different disciplinary and clinical backgrounds including medical care, patient groups, allergen manufacturers and regulators should be involved in the process of producing new data on standardized allergen preparations for the active treatment of FA.

Table 7 Gaps in the evidence for FA-AIT

Gaps in the evidence of FA AIT	Plan to address	Priority
Standardized products	Collaboration between clinical investigators, regulators.	High
Establish validated protocols with optimal dosing and duration of therapy	Analysis of existing data New observation and controlled trials Consensus discussion	High
Treatment of patient suffering from persistent allergies to multiple foods	Analysis of existing data New observation and controlled trials Consensus discussion	High
Definition of clinically relevant outcomes of effectiveness	Analysis of existing data New observation and controlled trials Consensus discussion with patients, clinicians and regulators Development and validation of relevant outcomes	High
Continued effectiveness after FA-AIT discontinuation	Analysis of existing data New observation and controlled trials Development and validation of relevant outcomes	High
Safety of FA-AIT during up-dosing and maintenance phases	Analysis of existing data Establish a standardized European registry of systemic adverse events New observation and controlled trials	High
Impact on QoL (patient-related outcomes)	Development and validation of relevant outcomes New observation and controlled trials	High
Cost-effectiveness	New observation and controlled trials	High
Advanced insight in the mechanisms of action	Collaborative research using biological samples (biobanks) of patients already treated. New observation and controlled trials	High
Identification markers of response	Analysis of existing data and biological samples New controlled trials	High
Identification the most suitable candidates (personalized care)	Analysis of existing data and biological samples New controlled trials	High
“Precision medicine” algorithms for patient tailored (individual) treatments	Analysis of existing data Consensus discussion	Medium
Standardized nomenclature according to clinical needs, newly developing treatments and mechanisms	Consensus discussion	Medium
Role of the different routes of administration	Randomised controlled trials	Medium
Effect of concomitant administration of anti-IgE on safety, efficacy and length of therapy	Analysis of existing data New controlled trials	Medium
Effect of concomitant administration of probiotics on safety, efficacy, and length of therapy	Controlled trials	Low

Novel therapeutic approaches are being developed to improve FA-AIT, most of them in pre-clinical or early clinical trials. In particular, co-administration of humanized monoclonal anti-IgE (omalizumab) seems to markedly reduce adverse reactions due to OIT compared to placebo (70-72). Furthermore, as bacteria are potent stimulants of Th1 immune

responses, modified bacterial products are under investigation as adjuvants for FA-AIT (46).

Clinical studies carried out with FA-AIT have some limitations, a key one is the heterogeneity in protocols between centers. It is yet unclear which duration and frequency of ingestion of the allergic food(s) is required to maintain desensitization. Furthermore,

Box 11 Key messages

- FA- AIT should be considered for children from around 4 - 5 years of age with symptoms suggestive of persistent IgE-mediated food allergy to cow's milk (Grade A), hen's egg (Grade B) or peanut (Grade A) plus evidence of IgE sensitization to the triggering allergen.
- The majority of children allergic to milk and egg develops tolerance spontaneously. For these patients, waiting to see if they outgrow their allergies, before initiating FA- AIT, represents a sensible option.
- Among FA-AIT routes, OIT affords better efficacy than SLIT; however OIT is associated with higher frequency of adverse events compared with SLIT; adverse events may occur either during build - up phase and with maintenance phase but most of them are not severe.
- Currently, for OIT FA-AIT the use of fresh material or native foods is advisable.
- Key contraindications are: poor adherence; uncontrolled or severe asthma, active systemic autoimmune disorders; active malignant neoplasia; eosinophilic esophagitis. Careful review of benefits and risks are required with active severe atopic dermatitis, chronic urticaria, cardiovascular diseases, beta-blocker or ACE inhibitor therapy.
- FA-AIT should be administered by competent personnel with immediate access to resuscitation equipment and a doctor trained in managing anaphylaxis.
- The initial FA-AIT dosage and each increased dosage during the build-up phase should be performed in clinical setting.

we are lacking criteria with which to evaluate and diagnose permanent tolerance. In AIT trials and in clinical practice, safety is of the paramount importance: strategies for improving safety during either up-dosing protocol or maintenance regimen need to be standardized. Managing these pivotal issues is mandatory for use of OIT/SLIT outside research settings or specialized clinical centers for FA-AIT.

FA-AIT should be utilized for patients with persistent food allergy (Box 11). In many patients, the downside of the adverse events associated with treatment is outweighed by both the achievement of desensitization and the reduced risk of a serious allergic reaction by accidental exposure at home or in the community. Considering the current evidence, there are still considerable knowledge gaps about how best to perform FA-AIT and more well-designed AIT trials are required.

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